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Laboratory and Human Studies on Polychlorinated Biphenyls (PCBs) and Related Compounds

by Renate D. Kimbrough*

Similar qualitative toxic effects have been observed in animals for a class of halogenated aromatic compounds, which include the halogenated biphenyls, naphthalenes, dibenzodioxins, and dibenzofurans. All of these compounds are lipid soluble and persist in the environment and in mammals. The polybrominated biphenyls (PBBs) are the most persistent. They are predominantly stored in fatty tissue; they pass the placenta and are excreted in milk. Some isomers of the halogenated biphenyls are more toxic than others. With some exceptions, the more toxic isomers are retained longer in tissues and are also the carcinogenic components of the mixture. Most of these chemicals seem to be promoters of carcinogenesis in animals rather than initiators. An array of toxic effects in laboratory animals has been ascribed to these compounds and numerous reviews summarizing this information are available. Less information is available on the human health effects of environmental and occupational exposure. Results of recent studies in animals to further elucidate the effects of these chemicals are presented, and results from some human studies conducted in the United States are reviewed.

Introduction

Concern about the chronic toxicity of organic chlorinated chemicals developed only in the last two decades (*1*). It was established in the 1950s that 1,1'-(2,2,2-trichloroethylidene)bis(4-chlorobenzene) (DDT) was retained in tissues (*2*), but this retention was not really considered to be harmful. The persistence of polychlorinated biphenyls (PCBs) in the environment was recognized in 1966 by Jensen (*3*), and 2,3,7,8-tetrachlorodibenzodioxin was first identified in 1957 (*4*). During this time, these types of chemicals were increasingly produced, and they and their wastes began to enter the environment (*5*). Around 1970, a chemical company in Michigan manufactured the brominated biphenyls as flame retardants. This same company also produced magnesium oxide, a chemical commonly mixed into feed for livestock. The flame retardant was called Firemaster and the magnesium oxide, Nutrimaster. In 1973 some bags of Firemaster were accidentally sold as Nutrimaster and mixed into animal feed; this resulted in widespread contamination in the State of Michigan (*6*). The production of brominated biphenyls has since been discontinued in the United States. The Michigan population has also been exposed to PCBs. Similarly, in a recently completed study (*7,8*) in a predominantly black population with exposure to high levels of DDT residues through the consumption of contaminated fish, elevated blood PCB levels were noted. Thus, in studying such population, multiple chemical exposure is usually encountered. As our analytical capabilities improve, chlorinated dibenzodioxins and dibenzofurans are detected in our environment with increasing frequency.

As in the case of polybrominated biphenyls (PBBs), little is usually known about the health effects of these chemicals when human exposure first occurs, nor, in every instance, are the combined effects of these different types of chemicals known. For these reasons, animal studies are begun at this point. If the animal studies suggest that the chemicals in question might, indeed, cause chronic health effects in humans, much energy is devoted to refuting the results. It would be more fruitful to try to determine, in unintentionally exposed populations, whether similar effects might occur. Because of the long life span in humans, such studies are difficult and expensive, and they do not provide quick answers. However, to elucidate the significance of laboratory animal studies, it is extremely important to determine whether chronic health effects occur in populations accidentally or occupationally exposed to these chemicals. It is equally important to

*Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA 30333.

recognize the limitations of such studies and to design them so that the results are meaningful.

Animal Studies

General

The chlorinated biphenyls, dibenzodioxins and furans have, as a group, been shown to affect reproduction, suppress the immune response, cause tumors in laboratory rodents, produce hepatic porphyria and cause chick edema in chickens. In the nonhuman primate, the rabbit, the horse, cattle and the hairless mouse, skin lesions can be produced which primarily involve hair follicles and Meibomian glands. The hair follicles dilate and fill with keratin, and the sebaceous glands atrophy. In addition, a variety of biochemical effects have been determined, and microsomal enzymes may be induced not only in the liver but also in other organs.

Not all animal species respond to these chemicals in the same way, nor do those organs showing the highest tissue concentrations of these compounds necessarily show the most pathology. In addition, different species vary in their susceptibility to the damaging effects of these chemicals. The monkey, guinea pig, and the mink are affected at much lower dosage levels than the rat, hamster and mouse. All of these chemicals are retained in the body for extended periods. A number of reviews on the toxicity of these compounds have appeared, and this information was summarized recently (*1,9,10*).

As far as chronic human health effects are concerned, the questions of whether these chemicals are carcinogenic, whether they are immunotoxic, and whether they affect reproduction are extremely important. Further, recent experimental evidence suggests that they may cause lipid peroxidation (*11*).

Both PBBs and PCBs are a mixture of chemicals. Within the last few years much progress has been made in characterizing these mixtures. It is now known that some isomers of these mixtures are much more toxic than others. The more toxic isomers are, generally, also the more persistent, both in the environment and in living organisms (*12–14*). Since PCBs were found usually to contain trace amounts of chlorinated dibenzofurans, some investigators have postulated that the toxic effects resulting from technical PCBs are caused by the chlorinated dibenzofurans. More recent research suggests that some PCB congeners are quite toxic by themselves. Thus, in comparing the toxicity of PCB mixtures, it is important to establish not only the concentration of chlorinated dibenzofurans in the mixture, but also the isometric composition of the mixture.

All of these chemicals are lipid soluble and are, therefore, primarily retained in adipose tissue, but they can also be measured in serum, at lower concentrations than in adipose tissue or in other organs. They pass the placenta and are primarily excreted through bile and milk. The ratios between adipose tissue, blood, and vital organs vary a great deal and are influenced by exposure level, sex, age, lipid content, length of exposure, and whether exposure is current. Furthermore, at very low concentrations, an analytical imprecision influences the ratio much more than at higher concentrations. Polarity also affects partitioning (*15,16*).

Immunotoxicity

There are two distinct but not entirely independent systems of immunity, the cell-mediated immunity and the humoral immunity (*17*). The cell-mediated immunity includes the following processes: the classical cell-mediated immunity against fungi, viruses and bacteria; the delayed-type hypersensitivity (e.g., tuberculin hypersensitivity); and the rejection of tumors and foreign tissue, such as transplants, and the allogenic (graft vs. host) diseases. The other system is the humoral immunity which operates through antibody-producing cells.

Neonatal thymectomy or radiation of the thymus impairs cell-mediated immune responses. The halogenated aromatic compounds discussed here are now thought to have a similar effect. In the guinea pig, the developing and the adult animal seem to be quite sensitive to this effect, but in other species, young animals are much more susceptible. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) has been the most extensively studied representative of this group. Guinea pigs exposed to as little as 40 ng TCDD/kg body weight weekly for 8 weeks had depressed delayed hypersensitivity reaction to tuberculin (*18*). The graft versus host reaction was suppressed after dosages of 0.5 μg/kg body weight weekly for 4 weeks.

Sharma et al. (*19*) reported that a number of immunological parameters were affected in mice and rabbits at dosage levels of less than 1 μg/kg/week for 8 weeks. The effects are more severe when the chemical is administered during both the prenatal and postnatal periods than during the postnatal period alone (*20–22*).

The expermental results for PCBs are not as clear-cut(*23*).

Both the cell-mediated and humoral immune responses were affected in some studies but not in others. The dosages of commercial PCB mixtures employed ranged from 0.3 mg to as much as 1000 mg/kg body weight. The differences in response are at least partly caused by differences in the composition of the mixtures. Isomers such as 3,4,3′,4′-tetrachlorobiphenyl, 3,4,5, 3′,4′,5′-hexachlorobiphenyl and 3,4,5,3′,4′-pentachlorobiphenyl are known to cause atrophy of the thymus and spleen in rodents. A pronounced immunotoxic effect depends most likely on the presence of these types of chemicals in the mixture (*24*).

Similarly, the PBB mixture contains isomers of varying degrees of toxicity. Thus far, these isomers have not been tested for their immunotoxic effects. The PBB mixture itself has, however, been shown to cause atrophy of the thymus and spleen in laboratory animals and to affect the immune response (*25*).

It has also been determined that exposure of 2,2′,4, 4′,5,5′-hexabromobiphenyl to ultraviolet light severely

increases its toxicity (*26*). Similar photolysis products have been identified in PBB-contaminated soil from Michigan (*27*).

Reproduction

Although TCDD has been shown to produce cleft palates in several strains of mice and subcutaneous edema, hemorrhage, and dilated renal pelvises in rats and mice, the other chemicals in this general group are not teratogenic, but they are fetotoxic (*1*). Mixtures of PCBs and PBBs have causes absorptions, abortions, and stillbirths and reduced survival to weaning in rodents, monkeys and mink. The monkey and the mink are affected at much lower dosage levels (*28*). Again, quantitative differences exist between different commercial mixtures. In multigeneration reproduction studies (*29*), a dietary level of 500 mg/kg body weight of a commercial PCB mixture of Aroclor 1260 has been found to be the lowest dose to affect reproduction in Sherman strain rats, but a dietary level of 20 mg/kg affected reproduction when Aroclor 1254 was fed. Thus, variation in the isomeric composition of different mixtures greatly influences results. Specific isomers of PBBs and PCBs have not been studied to any great extent (*14*), except in relation to enzyme induction and in *in vitro* tests. Since the isomeric composition of these chemicals changes in the environment, studies with commerical products may not be altogether relevant for predicting human health effects resulting from environmental exposure to these compounds. These chemicals are excreted in milk. Excretion in milk depends on its fat content, and the level of excretion would be much higher in rodents with a fat milk content of 13 to 15% than in humans, with 1 to 4%. Both species can, however, eliminate a large proportion of their body burden through milk and pass it on to their offspring.

All the compounds discussed here, including certain homologs of the PBB mixture, are extremely persistent in mammals. In a recent study, dams of Sherman strain rats were given two doses of 200 mg/kg of PBB by gavage during pregnancy. The offspring that were also nursed by the treated dams still had measurable PBB body burdens at the end of their life span (see also carcinogenesis) (*30*). At this dosage level, both the number of live pups born and the number surviving to weaning were slightly reduced. Similar studies have not been conducted with PCBs.

Carcinogenesis

A number of studies have been conducted with TCDD (*31,32*). Hepatocellular carcinomas and squamous carcinomas of the oropharynx and lungs were produced in Sprague-Dawley rats at doses of 0.1μg/kg/day. At daily doses of 0.07 μg/kg body weight, Osborne Mendel rats developed hepatocellular carcinomas and tumors of the thyroid. In Swiss mice, and B6C 3F1 mice, hepatocellular carcinomas were also produced, and after dermal exposure Swiss mice developed subcutaneous sarcomas. Although TCDD causes a variety of tumors, only liver tumors and—in one study—tumors of the stomach have been induced with PCBs. Kimbrough et al. (*34*) exposed female Sherman rats to dietary levels of 100 mg/kg Aroclor 1260 and found 26 hepatocellular carcinomas in 184 exposed rats, whereas only one of 173 controls had a hepatocellular carcinoma. In addition, many exposed rats had neoplastic nodules. In a study conducted by the National Cancer Institute (NCI) (*32*) with Aroclor 1254, there were 24 animals per group. Investigators gave three different dosage levels of 25, 50, and 100 ppm Aroclor 1254 to the rats over their life span. About 17 to 20 rats per group survived. At the low dose, neoplastic nodules were seen in 5 males. At the intermediate dose, they were present in 8, and at the high dose, in 12. In the females at the low dose, neoplastic nodules were present in 6; at the mid dose, in 9; and at the high dose, in 17. In males, one hepatocellular carcinoma was seen at the mid dose and two at the higher dose. In the females, no hepatocellular carcinomas were seen.

In the NCI study, a number of exposed rats had adenocarcinoma of the stomach. Morgan et al. (*35*) reexamined 191 stomachs of rats from this study, of which 144 rats had been exposed to Aroclor 1254. With different staining techniques, they found six adenocarcinomas in exposed rats, and observed a high incidence of squamous metaplasia in the epithelium of the stomach. Squamous metaplasia is associated with the occurrence of adenocarcinoma in the stomach. The rat strain used was Fisher F344. Adenocarcinoma of the stomach in this rat strain is extremely rare, 1 in 1754 (0.05%). Therefore, the investigators concluded that the likelihood of observing 6 adenocarcinomas in 144 rats was less than 0.05 ($p<0.05$). Preston et al. (*36*) found that PCBs promoted the induction of cancer initiated by diethyl nitrosamine.

In an additional study in Sprague-Dawley rats fed 100 ppm (100 mg/kg) Aroclor 1260, in which 32 male control, 49 female control, 46 male exposed, and 47 female exposed rats were available for microscopic examination, a high incidence of well-differentiated hepatocellular carcinomas was found in female rats and a lower incidence in males (*37*). In addition, a few Japanese PCBs were shown earlier to cause liver tumors in rodents (*38,39*).

As noted previously, PBBs are extremely persistent. It was possible to give 2-month-old female Sherman strain rats a single dose of 1000 mg/kg PBB by gavage and still find PBB levels ranging from 8.77 to 25.8 mg/kg in the liver on a wet weight basis about two years after exposure. The lipid concentration in these livers ranged from 1.9 to 7.3%. These rats had a 41.4% (24/58) incidence of trabecular carcinomas of the liver, whereas the controls had none. If the PBB was given in divided doses of 100 mg/kg twice a week every 3 weeks for a total of 12 doses, the incidence of trabecular carcinomas of the liver was higher (60.7%). Some hepatocellular carcinomas were very anaplastic, and one metastasized to the lungs (*40*). Others have also reported the induc-

tion of hepatocellular carcinoma in rats when PBB was fed in the diet for 6 months (*41*). Particularly in female rats, many of the animals with liver tumors also have hepatic porphyria caused by the inhibition of uroporphyrinogen decarboxylase. However, the two processes appear to be independent of each other. In a reproduction study in Sherman strain rats where the dams received two doses of 200 mg/kg PBB by gavage, the male offspring, at the end of their life span, had a 9.6% (4/41) incidence of hepatocellular carcinoma and the female offspring, an incidence of hepatocelular carcinoma and the female offspring, and incidence of 5.9% (3/51). No such tumors were seen in the controls, and none of the exposed offspring had hepatic porphyria. In addition to the hepatocellular carcinomas, neoplastic nodules were observed in 17.6% exposed females and in 4.9% exposed male rats. All exposed rats gained less weight, and the lifespan of the male rats appeared reduced in that many male rats died earlier than the controls (*30*). It is therefore possible to induce hepatocellular carcinomas in offspring of dams treated with PBB. No such studies have been conducted with PCBs to determine whether transplacental and neonatal exposure is associated with a reduced life span and an increased incidence in cancer. This study tends to support the claim (*42*) that promoters of carcinogenesis accelerate aging and thus reduce the life span.

Human Studies

The discussion of human studies will be primarily limited to PCBs and PBB.

Body Burdens

In the United States today the primary source of PCB exposure for the general population is fish from contaminated waters. In the past, some farm families were exposed to PCB from dairy products. The PCBs originated from paint used on the inside of silos. In addition to this kind of environmental contamination, workers who repair transformers and workers who handle toxic wastes may be exposed. Until 1976, occupational exposure also occurred through the production of PCBs and the incorporation of PCBs into transformers, capacitors and other commercial products.

Numerous investigators have reported PCB in human tissues (*43,44*). Because of regulatory actions taken in the United States, total environmental PCB contamination has dropped. However, it has been postulated that this merely represents a shift to a higher concentration of more toxic isomers and that for correlating PCB exposure with health effects, total PCB levels in serum or tissues are meaningless unless the isomeric composition of the PCBs have been characterized. In the United States, according to CDC data, mean blood PCB levels are about 5 to 7 ng/mL (pbb), although some patients may have higher blood levels without any documented unusual exposure. Levels in adipose tissue and in human milk fat are 100 to 200 times as high, since PCBs are highly lipid-soluble.

Recently, the predominantly black population of Triana, a small rural southern town in the United States, was studied (*7,8*). This population had had excessive exposure to DDT residues through the consumption of contaminated fish. Fish consumption correlated positively with PCB blood levels and no other source of PCB exposure could be established. These researchers also noted that PCB serum levels increased with age and that levels were lower in females of each age group. Similar findings were made for DDT residues. The serum cholesterol level was positively associated with the log PCB level independent of age, sex, fish consumption, body mass index, and alcohol consumption. Rates of borderline and definite hypertension for study participants were 30% higher than expected on the basis of national rates (*45*). Log PCB serum values made a significant contribution to explaining the variability of log systolic and diastolic blood pressure in multiple regression analysis (*46*).

In the United States, in males and females, median total cholesterol levels increase with age from about 150 to 160 mg/dL at age 20 to over 200 mg/dL at age 50. It is not entirely clear how much the concentration of PCB in blood is influenced by the serum lipid content and whether populations with inherently lower total serum cholesterol levels would have a different PCB serum adipose tissue ratio than populations consuming a western diet. The age-associated increase in blood PCB levels could be related to the long half-life of some PCB isomers which are preferentially retained in mammals (*47*), and as long as exposure continues, a true steady state between intake and excretion is never reached. Other variables affecting body burdens may be differences in metabolism with age. In the Triana studies (*7,8*) the blood levels of total DDT residues also increased with age, and others have made similar observations (*48-50*).

In a study of a population in Michigan (*51*), PCB blood levels again increased with age and were lower in females. This same population had exposure to PBB over a 2-year period in 1973 and 1974. The 1977 serum PBB levels in 3683 participants ranged from less than 1 to 3150 μg/l, with a geometric mean of 4.1 μg/l. Females had generally lower serum PBB levels than males, but mean serum PBB levels did not increase with age. The fact that PBB levels did not increase with age in the same population as did the PCB does not support the hypothesis of an age-related change in serum/adipose partition for these halogenated hydrocarbons. Length of exposure appears to be the determining factor (*51*).

The fact that PCB body burdens increase proportionally to the length of exposure is further supported by a study in workers. Wolff et al. (*52*), found that the partition in adipose tissue of approximately 120 to 160 times the plasma concentration is consistent with the higher lipid content of adipose tissue and that there is a good correlation between blood and adipose tissue PCB levels. Chase et al. (*53*) also found a positive association

between length of employment and blood and adipose tissue PCB levels.

Similarly, a significant correlation between serum PBB and adipose tissue PBB was found (*54*). Pregnant and nonpregnant women and chemical workers had similar serum to adipose tissue concentration ratios, which ranged from 1:140 to 1:260. Males from farms had significantly different ratios of 1:325 to 329. There is no obvious reason for these differences. In this study it was also found that PBB concentration in cord blood was one-tenth of that found in maternal serum. Human milk lipids contained PBB 107 to 119 times the amount present in maternal serum. All of these data suggest that serum levels of these types of chemicals can be considered to represent a fraction of the total body burden. If the serum concentrations are known, adipose tissue levels or levels in other organs can be estimated.

Very few human tissue samples have been analyzed for chlorinated dibenzodioxins. Most of the analyses have been limited to the determination of one isomer, 2,3,7,8-tetrachlorodibenzodioxin. Concentrations of this isomer in adipose tissue from the general population have been nondetectable or in the low nanogram per kilogram adipose tissue range. Since this compound is more polar than PCB and PBB, partitioning between adipose tissue liver and blood may be different, with less of a gradient between adipose tissue and blood.

Epidemiology Studies

Partly because of the Yusho episode in Japan and partly because of the animal toxicology data, a number of cross-sectional studies have been conducted in workers exposed to PCBs, and results of three mortality studies have been published. In addition, surveys have been conducted in populations that have had environmental exposure. In all of these studies the number of participants was limited (*7,8,46,55–61*), and most were cross-sectional studies, which are limited in their ability to evaluate chronic health effects.

In a number of studies, a positive association between results of one liver function test in particular, the test for γ-glutamyltranspeptidase, and PCB blood levels has been found. In addition, a positive association also seems to exist between blood PCB levels and either triglyceride and/or cholesterol serum levels (*7,53,56,62*). The significance of these findings is not clear. A possible explanation is that the liver is impaired in its ability to transport, metabolize, or in other ways handle lipids properly. Increased serum cholesterol levels have also been reported in animals following exposure to PBB and PCB (*11*), whereas serum triglycerides were unaffected. Bernert et al. (*11*) also found enhanced lipid peroxidation. No attempts have been made to determine whether these chemicals cause lipid peroxidation in humans.

Published reports have shown that these types of compounds affect reproduction in animals but, except for the studies of Yusho patients, there are no published reports on how PCBs affect reproduction in humans. Taylor (*63*) presented preliminary data of a comparison study of neonatal birth weight and gestation period of infants from women who worked in capacitor plants. When these two outcomes were compared with those in workers in the same plant who were not exposed to PCBs, differences were noted. Although the exposed group was small, the gestation periods were shorter, and the birth weights lower. The lower birth weight could be explained in part by the shorter gestational period. The study emphasizes that reproductive outcomes need further study.

Thus far, no such findings have been reported from a study in a population inadvertently exposed to PBB in Michigan (*51*). This exposure occurred in 1973 and 1974, and the Michigan Department of Health, in collaboration with the Centers for Disease Control, has enrolled about 4000 people in a long-term prospective study, begun in 1976. Blood PBB levels have been determined for all participants, and data have been collected by questionnaire. In addition, some participants have had more in-depth studies, the results of which have not been completely analyzed. No effects on reproductive outcomes have been observed in this cohort, but the number of newborns in this group has been small, and many of the participants have had very low level exposure. Other confounding variables, such as smoking and alcohol consumption, may also contribute to adverse reproductive outcomes. Another problem is that exposure may not have been properly defined, since some PBB isomers, particularly photolysis products, are much more toxic than other congeners of the mixture. However, only total PBB levels have been determined in the population, and no attempt has been made to characterize the PBB. It is conceivable that people with symptoms might have been preferentially exposed to the more toxic isomers. Thus, correlating symptoms with total PBB levels may not be valid.

In a study in which organochlorine compounds were measured in patients who had died of cancer and patients who died of other diseases (*64*), higher concentrations of PCB and DDE were found in the samples for the cancer patients. The mean PCB adipose levels in 11 male cancer patients was 8.8 mg/kg and in 22 noncancer patients, 5.9 mg/kg. Although these differences are not large, they were statistically significant. Wassermann et al. (*64*) reported an increased concentration of organochlorine compounds in lipids extracted from malignant breast tissue compared with those from adjacent, apparently normal breast tissue. Many factors, such as age nutritional status, medications and precision of the analytical methods, can influence levels of organochlorine in tissue. The significance of these observations is not clear, particularly since they are within the range of levels normally observed in the general population.

Only three attempts have been made to determine whether exposure to PCBs causes an increased incidence of cancer. First, a retropsective mortality study of 2567 workers in two capacitor plants was conducted by Brown et al. (*60*). There were relatively few deaths (163), which severely limited the statistical power of the study, and the average follow-up was only 15 years,

whereas latency periods of 20 to 30 years are not uncommon for cancer deaths. The power of the study to detect, for instance, a twofold increase in liver cancer was approximately 13%. Over 50% of the sample had exposure to PCB for only 2 years or less. Deaths from liver cancer, cirrhosis of the liver and rectal cancer were slightly higher than expected, but this was not statistically significant for both sites combined. The observed increase for cancer of the rectum was statistically significant among females at one of the plants. Additonal mortality studies are in progress, but results are not yet available. Second, Bahn et al. (*59*) reported earlier three melanomas and two carcinomas of the pancreas in 41 refinery plant employees and 51 research and development workers. This incidence was significantly higher than expected. The cohort was again rather small, and these workers had also had exposure to other chemicals.

Third, Bertazzi et al. (*61*) reviewed the mortality of 290 males and 1020 females who had worked for 6 months or more in capacitor production. Males had a statistically significant increased number of deaths from all neoplasms. When analyzed by organ system, deaths from neoplasms of the digestive system, the peritoneum, the lymphatic, and hematopoietic tissues were higher. Among females, all causes of deaths were significantly elevated. However, the actual numbers in this study were small, and further studies are needed to substantiate these findings.

Occasionally, in spite of the documented toxicity in animals, it is suggested that chloracne is the only established health effect in humans following exposure to TCDD.

When such statements are made, findings, such as porphyria cutanea tarda (*66,67*) and other systemic health effects (*1*) are largely ignored. However, it is not clear whether TCDD causes porphyria cutanea tarda in humans. Neither is it pointed out that in all of the episodes where workers developed chloracne the actual amount of TCDD that they absorbed or were exposed to is unknown. Again, in each of these episodes, the actual numbers of exposed workers are too small to yield useful information about possible chronic health effects. The largest of these followup studies was that of 121 workers by Zack and Suskind (*68*). The National Institute of Occupational Safety and Health has established a registry of workers with chloracne for a prospective followup study, and the World Health Organization will follow all such workers prospectively on a worldwide basis. Virtually no information is available in the literature on the other chlorinated dibenzodioxins. Occasionally, chloracne and respiratory symptoms have been reported in workers exposed to pentachlorophenols (*69*), but it is not known to what extent and with what isomers of chlorinated dibenzodioxins and chlorinated dibenzofurans the pentachlorophenols were contaminated.

Hardell et al. (*70*) and Erikson et al. (*71*) conducted two case control studies in Sweden and reported an increased risk of soft tissue sarcomas in men who were exposed either to trichlorophenols or to phenoxy herbicides during their application. These authors also reported a third case control study from Sweden which suggests that phenoxy acids and chlorophenols may also predispose to Hodgkin's lymphoma, but as yet there is little support for this theory from other sources (*72*). The Swedish studies were recently summarized and discussed by Coggon and Acheson (*73*), who concluded that "Further research is urgently needed to confirm or refute these associations, to define the extent of the risk (if any) and to identify the carcinogen(s)."

In the U. S. the Swedish results could not be substantiated by Milham (*74*) but are supported by results (*75,76*) in production workers. In the U.S., four followup studies were conducted among workers exposed to 2,4,5-trichlorophenol or 2,4,5-T. Each of three cohorts had one death due to soft tissue sarcoma. Honchar and Halperin (*75*) reviewed the four studies and noted that in the four merged cohorts there were a total of 105 deaths, three of which (2.9%) were due to soft tissue sarcoma. Based on national rates of death for men aged 20 to 80, only 0.07% of deaths due to soft tissue sarcoma would have been expected. Recently another person in one of the four cohorts died due to a soft tissue sarcoma (*76*), bringing the total to four deaths due to soft tissue sarcoma in the four merged U. S. cohorts. Microscopic review of tissue sections from these tumors and three additional cases was recently done. Two of the four cases with documented evidence of exposure and three additional cases that did not have documented evidence of exposure were confirmed to represent soft tissue sarcoma (*77*). Further large epidemiology studies must be completed before the soft tissue sarcoma issue can be resolved.

Since exposure to PBB took place only about 10 years ago, the follow-up period in the Michigan cohort is too short for results to be meaningful. In addition, the actual number of participants that are followed may not be large enough to detect small increases in cancer. Since the cohort is composed of participants who have been exposed to widely varying amounts of PBB, this becomes even more unlikely.

Conclusions

Animal studies seem to indicate that PCB, PBB, and related compounds severely affect reproduction, are carcinogenic—most likely acting as promoters—and have immunotoxic effects. They also seem to cause lipid peroxidation, increase serum cholesterol levels, and, in some species, produce liver toxicity.

In humans, no adequate studies have been conducted to judge whether long-term exposure to PCB is associated with cancer, nor have any reports been published which have properly studied reproductive outcomes of highly exposed females. On the other hand, it has been determined that as long as exposure to PCB occurs, body burdens will increase and the more toxic congeners of the mixture will be preferentially retained. Higher blood PCB levels are associated with higher serum triglyceride and/or cholesterol levels, and in a

study in which blood pressure was measured, high blood pressure was associated with higher blood PCB levels. It is important that additional studies be done with sufficient statistical power to detect an increase (doubling) in cancer. This will probably be possible only if a number of exposed cohorts are combined. Consideration should be given to establishing such a group among highly exposed sports fishermen and their families, since their exposure would be consistent with environmental rather than occupational exposure. Reproductive outcomes might also be more easily studied in such groups.

Hypertension is very prevalent in the United States and greatly influenced by lifestyle. Studies are needed to determine the significance of the association between blood PCB levels and elevated blood pressure.

Other well-designed studies are needed to determine the human health effects of chlorinated dibenzodioxins.

Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or by the U.S. Department of Health and Human Services.

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